

REMARKS

Claims 1-26 were pending in the present application. Claims 14-20 have been withdrawn.

Applicant has amended claims 1, 3, 4, 6, 9, 10, 13, 23 and 24, without prejudice. Applicant reserves the right to pursue any deleted subject matter in one or more continuing applications.

The claim amendments have been made to correct editorial errors and/or to improve clarity. Specifically, claim 1 has been amended to correct a typographical error. Claims 3, 4, 9, 10, 23 and 24 have been amended to recite an approximate molecular weight instead of an improper range. Support for this amendment can be found in the specification (as published as U.S. Patent Application Publication No. 2007/0092526), for example, at paragraphs [0071]-[0072]. Claim 6 has been amended to include an abbreviation for a recited term. Support for this amendment can be found in the specification, for example, at paragraph [0021]. Claim 13 has been amended to recite the components of the specified formulations. Support for this amendment can be found in the specification, for example, at paragraph [0088] and Table 7.

No new matter has been added by these amendments.

After entry of the amendments, claims 1-26 will remain pending.

Applicant respectfully requests entry of the foregoing amendments and consideration of the following remarks.

Applicant notes that, in reference C06 (Feinberg et al., "The Safety and Immunogenicity of Merck's HIV-1 gag DNA Vaccines (with or without adjuvants) in Healthy Adults", presented at AIDS Vaccine 2003), all references to CRL-1005 refer to a formulation containing 7.5 mg/ml CRL-1005 and 0.6 mM benzalkonium chloride.

Claim Rejections – 35 U.S.C. § 103

Claims 1-12 and 21-26 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over WO 96/04932 ("Balasubramanian") in view of WO 97/25072 ("Engler"). Applicants respectfully traverse.

The present invention is based on the inclusion of a cationic surfactant in a polynucleotide/non-ionic block copolymer formulation. The selected cationic surfactant results in (1) an increased percentage of polynucleotide that is physically associated with the block

copolymer/cationic surfactant adjuvant; and (2) an enhanced immune response to the polynucleotide. See the specification, for example, at page 2, line 32 to page 3, line 2.

Balasubramanian teaches high molecular weight nonionic block copolymers, for use as an adjuvant in vaccines, having the formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$ where the molecular weight is between approximately 7000 and 20000 Daltons, and (a) represents a number such that the percentage of polyoxyethylene hydrophile is between approximately 1% and 40% by weight. See Balasubramanian, pg. 5, lines 1-21. Balasubramanian also teaches compositions comprising genes, nonionic block copolymers having the formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$, a surfactant (such as Tween 80), and a low molecular weight alcohol. See id. at pgs. 51-52. As noted by the Examiner, Balasubramanian does not teach inclusion of a cationic surfactant.

Engler teaches gene-delivery systems formulated in a buffer comprising a delivery-enhancing agent such as a detergent or surfactant, including a cationic detergent such as benzalkonium chloride and cetylpyridium. See Engler, pg. 3, lines 11-14 and pg. 5, lines 1-24. Notably, when various detergents were tested for their ability to enhance gene transfer, the cationic detergents, benzalkonium chloride and cetylpyridium, did not enhance gene transfer. See id. at pg. 13, line 13 to pg. 14, line 2 and Table 1.

The Examiner contends that it would have been *prima facie* obvious to the skilled artisan at the time of the present invention to include a cationic detergent in the compositions of Balasubramanian comprising polynucleotides, a high molecular weight block copolymer adjuvant, and optionally a nonionic surfactant, in order to enhance delivery of polynucleotides because (1) one of skill in the art would have been motivated to use a cationic detergent to enhance delivery of a nucleic acid as taught by Engler; and (2) there would have been a reasonable expectation of success based on the high degree of skill in molecular biology and the detailed disclosures of Balasubramanian and Engler.

First, Applicant respectfully submits that there is no teaching, suggestion or motivation for the present invention.

The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh

the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991).

MPEP § 2143.01, 8th Edition, Rev. 6 (September 2007).

Balasubramanian teaches compositions comprising genes, nonionic block copolymers having the formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$, a surfactant (such as Tween 80), and a low molecular weight alcohol, but does not provide any data with compositions having a surfactant. Engler teaches gene-delivery systems formulated in a buffer comprising a delivery-enhancing agent such as a detergent or surfactant. Example 5 in Engler describes the effect of various detergents on gene transfer efficiency. See Engler, at pg. 13, line 11 et seq. Many of the non-ionic detergents, one of the anionic detergents, and none of the cationic detergents provided a significant enhancement in gene transfer.

Based on Engler's results with cationic detergents, one of skill in the art would not have been led to combining a cationic detergent with a high molecular weight non-ionic block copolymer. Rather, the lack of significant enhancement of gene transfer efficiency with cationic detergents teaches away from the combination¹.

Second, Applicant respectfully submits that there is not a reasonable expectation of success for using a cationic surfactant with a high molecular weight non-ionic block copolymer to improve gene transfer efficiency. Based on Engler's results, there is no basis for expecting that the combination of a high molecular weight non-ionic block copolymer and a cationic lipid would provide any increase in gene transfer efficiency².

For the above reasons, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 103.

¹ It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). MPEP § 2145, 8th Edition, Rev. 6 (September 2007).

² Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). MPEP § 2143.02, 8th Edition, Rev. 6 (September 2007).

Claim Rejections – 35 U.S.C. § 112

Claims 3-4 and 23-24 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner contends that the metes and bounds of claims 3 and 23, which recite the phrase "is between approximately 9000 Daltons", and claims 4 and 24, which recite the phrase "is between approximately 12000 Daltons", cannot be determined because use of the word "between" indicates a range.

In response, Applicants have amended claims 3-4 and 23-24 to delete the word "between". Accordingly, the rejection has been obviated.

Claim 13 was rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner contends that reference to formulations as "D118, D118a, and D121" in claim 13 is indefinite because the composition of these formulations is not clear.

Without admitting to the propriety of the rejection and in an effort to advance prosecution, Applicant has amended claim 13 to recite the composition of these formulations. Accordingly, the rejection has been obviated.

For the above reasons, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. 112.

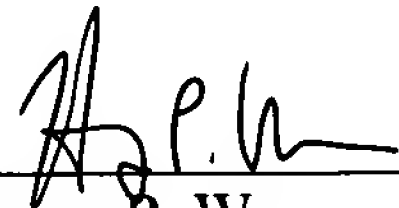
Serial No.: 09/888,304
Case No.: 20703Y

CONCLUSION

Applicants believe the claims are in condition for allowance. An early indication of the same is requested. The Examiner is invited to contact Applicant's Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

Date: April 23, 2008

By: 
Henry P. Wu
Reg. No. 44,412
Attorney for Applicant

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(732) 594-5312